HUMAN ARTERIOSCLEROSIS: SOME REMARKS CONCERNING ITS ETIOLOGY AND SYMPTOMATOLOGY.

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Etiology. Arteriosclerosis is another term for aging. It means that the vascular domain, especially the arterial portion, and also other tissue cells, are wearing out. There are some factors which we feel certain, and others which we suspect, speed up this aging process, yet in most instances we do not know the exact *modus operandi.* Among the factors which play an active part we find (1) the wear and tear of life, (2) infectious processes, (3) intoxications, (4) mechanical strain. The relative importance of these factors doubtless varies in individual cases, as does their relative importance, in the opinion of many observers who have given thought to the subject.

1. *The Wear and Tear of Life.* It is easy to grasp what is meant by this title. It is very difficult, if not impossible, in the present state of our knowledge, to accurately explain the concrete sequence of causes and events.

Our first thought, perhaps, suggests heredity. We know that certain organisms and machines are more enduring than others; more capable of adjustment to surrounding circumstances and more resistant to certain types of strain. But, unfortunately, we often cannot assign the reason, nor do we know the exact nature of the strain. The influence of heredity is quite as impossible to explain as is growth and longevity in different species of animals. Why does the swan live so much longer than the sparrow or the elephant than the mouse? Why do some individuals live to a ripe old age, having passed through hardships, physical strain, infectious disease, exogenous intoxications and severe trauma, while others succumb early and easily?

Oliver Wendell Holmes on being asked how a man should proceed in order to live to the age of seventy years, replied that he should pick his ancestors for one hundred years before he was born.

It is easy to show by mathematical formula the enormous and increasing strain to which the heart and arteries are subjected. Also that these strains may be and often are much enhanced by habits of life, such as severe muscular effort, and by causes such as chronic arterial hypertension. But, again, this leads us once more into the maze. Why the difference in individuals?

Some things, however, it appears do exercise profound effects. It is agreed that the modern high-tension life, kept under the spur by ambition and competition, with inadequate mental relaxation and with insufficient physical exercise, which helps to redistribute blood and relieve congested vascular areas, does much to produce arteriosclerotic changes.

2. *Infectious Diseases.* It has been said, with truth, that "Venus loves the arteries." One of the definite advances of our knowledge within recent years has been the frequency with which syphilis produces disease of the aorta. It appears that although the involvement of this vessel is a frequent if not constant, as well as an early lesion, its symptoms rarely manifest themselves with obtrusiveness for sixteen years. As an illustration of this the army experience may be quoted. Out of 1,000,000 men examined 11,562 were rejected for cardiovascular diseases, and among these only 20 men were found to have aortic aneurysm; even aortic insufficiency of luetic origin was not common. With syphilis as a known, important factor of arterial disease, and with the current estimate that about 15 per cent. of our population has been thus infected, many cases of arteriosclerosis are accounted for. Other infections, such as typhoid fever and tuberculosis, may also be held accountable for some cases. In addition to the clinical evidence, aortic atheroma has been produced by the experimental injection of various pathogenic bacteria in animals. Focal infections doubtless also play a role.

3. *Intoxications.* Lead, alcohol and tobacco are regarded as potent factors. In regard to the former there can be no question. Lead may act (*a*) directly upon the bloodvessels or indirectly through the production of (*b*) nephritis and (*c*) gout. The role of alcohol is more in doubt, and difficult to evaluate, owing to the coincident presence of other causes. As an important etiological factor alcohol *per se* has certainly lost caste in recent years. Perhaps our great national experiment may in the future throw light on this subject. Tobacco establishes a far better claim as a noxious agent than alcohol. Experimentally the injection of nicotin in small quantities increases the secretion of epinephrin. Arterial lesions are readily produced by the injection of nicotin, and blood-pressure changes can easily be demonstrated in human beings. In a certain type of arteriosclerosis, thrombo-angeitis obliterans, a Jewish heredity, and the cigarette have been especially incriminated. And yet when one considers the number of heavy users of tobacco who live to old age, one wonders how great a role tobacco plays.

4. *Mechanical Factors.* Arterial hypertension, often associated with nephritis, justly receives credit for many cases of arteriosclerosis. This may be more or less localized, as in the aorta and brachial arteries of the laborer, or in the cerebral sclerosis of the man who works with his brain. As a rule, however, the process is more generalized, although the heart or the brain may be the chief point

of attack. As Osler has said, "The tragedies of life are largely arterial."

5. *Chemical Factors.* The whole trend of modern medicine is toward chemistry. Is it not natural to turn to chemistry as an explanation of our riddle?

(*a*) *Auto-Intoxication.* Metchnikoff's conception of arteriosclerosis as a result of "auto-intoxication," due to production and absorption of poisonous products, putrefactive in character and arising from the intestinal flora, has attracted much attention. While the possibility of this hypothesis in some cases cannot be denied it certainly has not been proved to be a constant or even frequent factor.

(*b*) *Internal Secretions.* Attempts have been made to show that arterial hypertension and vascular disease may result from disturbance of the internal secretions. We know that the medullary part of the adrenal gland and the infundibular portion of the pituitary are potent vasoconstrictors. Arterial lesions are readily produced experimentally by the injection of epinephrin, although they differ in type from human arteriosclerosis. Much stress has been laid upon epinephrin as a factor in the causation of arteriosclerosis, it being believed that it acts chiefly by its effect on the vasa vasorum. Contraction or occlusion of these vessels would naturally impair the nutrition and resistance of the arteries. In some clinical cases of arteriosclerosis, disease of the vasa vasorum is the only change demonstrable. Such lesions may produce both intimal and medial necrosis. (Cowan.) Degenerative disease of the adrenal glands, as seen in Addison's disease, is associated with hypotension; but this line of reasoning apparently leads us astray, since the adrenal glands are, it appears, only emergency organs which are not concerned in the normal maintenance of blood-pressure, and an increased epinephrinemia cannot be shown to exist in chronic hypertensive disease. It is possible, of course, that an individual living under continued high tension, with periods of excitement and strain, may suffer some arterial damage from this cause, but that it is much of a factor cannot be maintained.

Again, the secretion of the thyroid gland exerts a marked influence upon the circulation, greatly increasing the work of the heart, the rate of blood flow and dilating the peripheral vessels. Arterial thickening is a pronounced feature in long-standing cases, as is also cardiac hypertrophy. It has been suggested that an excessive protein diet acts through its effect upon the thyroid gland. It being pointed out that the plethoric gourmand presents many symptoms similar to those of hyperthyroidism, such as flushing, a sensation of warmth, palpitation, nervous irritability, increased blood-pressure, etc. (Sajous.) There also appears to be an interrelation between the ovaries and other glands of internal secretion. Vasomotor disturbances are common at the time of the menopause, and arterial hypertension is often first manifested at this time. These and many other thoughts along this line are suggestive and interesting, but largely speculative and not explanatory of the basic cause of arteriosclerosis.

(c) *Protein Metabolism.* If then the chemistry which we speak of as endocrinology fails to solve the riddle of arteriosclerosis, can we turn to a more fruitful field, that of metabolic chemistry? In this domain we are equally at a loss for an answer. It is probable that certain products resulting from the digestion of protein or the products of metabolic activity—protein catabolism—may exercise deleterious effects upon the vascular system, but experimentally the products of hydrolysis and amine formation from protein are dilators of vascular structures. As an example, histidin, one of the common amino-acids, may be mentioned. Of course, it does not follow that only vasoconstrictors can produce arterial damage. Arterial lesions can be produced experimentally by the injection of toxins or epinephrin even if a rise of blood-pressure is prevented by the simultaneous injection of the nitrites. Clinically, it seems established that overindulgence in food, especially protein food, has deleterious results. Certainly, the withdrawal of proteins and the restriction of food generally to the point at which only the nutritive needs are supplied is often followed by a great ameliorization, if not an actual disappearance, of hypertensive symptoms.

SYMPTOMATOLOGY.

Bearing in mind the fact that arteriosclerosis is a general disease affecting not only the circulatory system, but probably also other tissues as well, it is not surprising to find that its symptoms may be practically coextensive with the ailments which flesh is heir to. It is equally obvious, inasmuch as arteriosclerosis is a normal biological development, which may begin at any age, that the early manifestations may be slight, vague, ill-defined and difficult to evaluate.

Many cases diagnosticated as indigestion, biliousness, neuralgia, neurasthenia, asthma, bronchitis are in reality the early manifestations of arterial disease. It is well to be skeptical regarding what appear to be purely functional derangements without demonstrable cause in individuals past middle life. It was doubtless with this or a kindred thought in mind that the following advice was offered by an experienced practitioner: "When the patient complains of his stomach, examine the heart; when he complains of his heart, examine the stomach." It is hardly necessary to recall the number of sudden deaths attributed to "acute indigestion."

It would profit but little to enumerate *in extenso* all the different symptoms which arteriosclerosis may occasion, but a few phases may perhaps merit allusion.

As is well known, sclerosis of the arteries is nearly always general, yet in a given case certain organs or systems are the chief sufferers. It is customary, therefore, to class the cases as (1) cardiac, (2) renal, (3) cerebral, (4) peripheral, (5) abdominal, (6) nervous. In each instance symptoms may arise as a result of spasm, diminution in caliber, thrombosis or rupture of a given vessel. Such symptoms are usually but not always brought on when an extra demand for blood, either locally or in other areas of the body, exists. Thus in the cardiac type one has as subgroups those in which (*a*) myocardial, (*b*) valvular and (*c*) coronary lesions and symptoms predominate the picture. In the renal group one finds (*a*) cases associated with the contracted kidney and often with very marked secondary vascular changes resulting from toxemia and hypertension, and (*b*) those cases which show the true red, beefy sclerotic kidney and often exhibiting few if any urinary symptoms. In the cerebral type one finds not only a loss of mental elasticity, an inability to concentrate attention or to enjoy things that once made an appeal; but also psychasthenic manifestations, vagaries of conduct or outbursts of excitement in people who had previously steered a straight course and kept an even keel. One also encounterers amnesias and temporary failure, either partial or complete, of vision, hearing or consciousness; also aphasias.

The peripheral type is chiefly exemplified by vascular spasm, intermittent claudication, spontaneous cramps, neuritic pain as in erythromelalgia, localized gangrene, etc.

We must speak with less assurance regarding the abdominal type. Most often one sees flatulent indigestion simulating cholelithiasis or ulcer. The latter may actually exist as a result of localized endarteritis. A special type of angina, angina abdominis, has been described.

Finally, in the nervous group one finds vertigo and even convulsions epileptiform in character. Such convulsions occurring in individuals past middle life, in the absence of syphilis, lead and uremia, usually have an arteriosclerotic basis.

Arteriosclerosis may occur in infants, and when one takes the trouble to look for it, it is not infrequently found in young adults who may at the time show no vascular symptoms The symptoms in these cases usually do not appear until arterial hypertension becomes an added factor, and this, in many instances, may be years after the peripheral arteries first show definite thickening.

But according to the modern conception, as has already been stated, arteriosclerosis is a general disease; general, not only in its arterial distribution but also in the fact that all the tissues of the body may show the effects of the disease even independently of the disturbances which result from a diminished blood supply. In other words, the chemical changes which cause vascular disease affect other tissue cells directly, just as they do the arterial walls.

Hence much attention has been focussed upon a so-called "presclerotic" stage. Only after this stage has advanced will one be able to demonstrate arterial changes. Still later, as the case progresses, definite evidences of circulatory, renal or cerebral failure, or a terminal infection, will appear upon the scene. In the first stage various and often ill-defined phenomena make their appearance.

The earliest stage is always difficult, sometimes impossible of recognition. Generally, one notes what appear to be a beginning loss of bodily vigor, resistance to strain, or to infection, either with or without what appear to be slight functional derangements, involving the digestive, circulatory, renal or nervous systems. Sometimes the only noticeable changes are those of the skin, which becomes dry, wrinkled and atonic, with a diminished sebaceous activity, a tendency to chap, and suggests a possible hypothyroidism. Or perhaps the patient may simply show an apparently causeless anemia.

There is in the minds of many much confusion between arterial hypertension and arteriosclerosis. Indeed, the terms are unfortunately sometimes used interchangeably. Of course, the two conditions are often simultaneously present and prolonged hypertension often leads to arteriosclerosis. But that the reverse is true appears more than doubtful. (1) To begin with we are confronted with the great senile group whose arteries may be like pipe-stems but whose pressures are practically normal; (2) we have the large group of hypertensive cases in whom the increased pressure begins in middle life, is maintained at a very high level and precedes by many years the appearance of demonstrable arterial thickening; (3) it is not conceivable that a splanchnic vascular spasm can be maintained over months and years of life, especially without producing more local intra-abdominal disturbances than is the case, to say nothing of the fact that splanchnic sclerosis is but rarely demonstrable at autopsy.

In conclusion, it seems that clinical arteriosclerosis may simply be an involutional process, a part and parcel of aging; or it may be mechanical or toxic in origin. Just how this involutional process is brought about we are not in a position to state. But it seems more than likely that it will ultimately be shown to be the result of chemical changes associated with the bodily metabolism, which exert their effects upon the individual visceral, vascular and somatic cells, either directly or through the mediation of the ductless glands.